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Objective Assessment of Adherence to Inhalers by COPD Patients.

Imran Sulaiman
Royal College of Surgeons in Ireland, imransulaiman@rcsi.ie

Breda Cushen
Royal College of Surgeons in Ireland, brendacushen@rcsi.ie

Garrett Greene
Royal College of Surgeons in Ireland, garrettgreen@rcsi.ie

Jansen Seheult
Royal College of Surgeons in Ireland, jansenseheult@rcsi.ie

Dexter Seow
Royal College of Surgeons in Ireland, dexterseow@rcsi.ie

See next page for additional authors

Authors
Imran Sulaiman, Breda Cushen, Garrett Greene, Jansen Seheult, Dexter Seow, Fiona Rawat, Elaine MacHale, Matshediso Mokoka, Catherine Nora Moran, Aoife Sartini Bhreathnach, Philippa MacHale, Shahed Tappuni, Brenda Deering, Mandy Jackson, Hannah McCarthy, Lisa Mellon, Frank Doyle, Fiona Boland, Richard B. Reilly, and Richard W. Costello

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Objective assessment of adherence to inhalers by COPD patients

Imran Sulaiman[1], Breda Cushen[1], Garrett Greene[2], Jansen Seheult[1], Dexter Seow[1], Fiona Rawat[1], Elaine MacHale[1], Matshediso Mokoka[1], Catherine Nora Moran[2], Aoife Sartini Bhreathnach[1], Philippa MacHale[1,] Shahed Tappuni[1], Brenda Deering[3], Mandy Jackson[1], Hannah McCarthy[1], Lisa Mellon[2], Frank Doyle[2], Fiona Boland[4], Richard B Reilly[5, 6,7], *Richard W Costello RW[1, 8]

1. Clinical Research Centre, Smurfit Building, Beaumont Hospital, Royal College of Surgeons in Ireland , Dublin, Ireland

2. Department of Psychology, Royal College of Surgeons in Ireland, Dublin, Ireland.

3. COPD Outreach, Beaumont Hospital, Dublin, Ireland

4. Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland.

5. Trinity Centre of Bioengineering, Trinity College, The University of Dublin, Ireland

6. School of Engineering, Trinity College, The University of Dublin, Ireland

7. School of Medicine, Trinity College, The University of Dublin, Ireland

8. Department of Respiratory Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

*Corresponding author
Richard W Costello
Royal College of Surgeons in Ireland,
Beaumont Hospital
Dublin 9
Ireland
+353874176928
rcostello@rcsi.ie

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Of note, RWC and RBR are named on a patent for the INCA^{TM} device.

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What is the current scientific knowledge on this subject?

For patients with severe chronic obstructive pulmonary disease (COPD), inhaled preventer therapy reduces exacerbations of COPD. Hence, when a patient with COPD is discharged from hospital, it is assumed that they continue their treatment to avoid re-admission. However, objective adherence, including technique of use, to inhaler therapy via the Diskus™ has not been previously studied in this patient population.

What does the study add to the field?

Using an acoustic based system to quantify when and how a Diskus™ inhaler has been used, this study identified that the Actual Adherence over the study was 22.9% of what would be expected if all the doses had been taken correctly and on time. Only 7% of the study population had an Actual Adherence over 80%. Adherence was negatively influenced by impairment in cognitive function and the degree of airways obstruction.

"This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org"

ABSTRACT

Rationale

Objective adherence to inhaled therapy by patients with COPD has not been reported.

Objectives

The aim of this study was to objectively quantify adherence to preventer Diskus™ inhaler therapy by patients with COPD with an electronic audio recording device (INCA™).

Methods

This was a prospective observational study. On discharge from hospital patients were given a salmeterol/fluticasone inhaler with an INCA™ device attached. Analysis of this audio quantified the frequency and proficiency of inhaler use.

Measurements and Main Results

COPD patients (n=265) were recruited. The mean age 71 years, mean Forced Expiratory Volume in 1-second 1.3 Litres, and 80% had evidence of mild/moderate cognitive impairment.

By combining time of use, interval between doses and critical technique errors, thus incorporating both intentional and unintentional non-adherence, a measure "Actual Adherence" was calculated. Mean Actual Adherence was 22.9% of that expected if the doses were taken correctly and on time. Seven percent had an Actual Adherence>80%. Hierarchical clustering found three equally sized well-separated clusters corresponding to distinct patterns: Cluster 1 (34%) had low inhaler use and high error rates, Cluster 2 (31%) had high inhaler use and high error rates, and Cluster 3 (30%) had overall good adherence. Lung function and co-morbidities were predictive of poor technique, while age and cognition with poor lung function distinguished those with poor adherence and frequent errors in technique.

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Conclusion

These data may inform clinicians both in understanding why a prescribed inhaler is not effective and to devise strategies to promote adherence in COPD.

Word Count = 247

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common chronic condition characterised by airflow limitation, which can be controlled with inhaled corticosteroids (ICS) (1). Prior studies, have shown that between 30 to 60% of patients do not regularly collect their prescriptions (2). Some studies have also reported poor inhaler adherence in hospitalised patients (3-5). In addition, it is recognised that inhaler technique is poor among patients with COPD, which means that even when the medication is taken, a clinical response may not be achieved (6,7).

Some of the current techniques for monitoring adherence include patient self-report and pharmacy refill records; however, these techniques are limited. With self-report some patients may have difficulty remembering medication use, while pharmacy refill records provide information on whether the prescription has been filled and not whether the individual has actually taken the medication. Electronic monitors can objectively assess inhaler adherence as seen in several published papers (8-11). Most electronic monitors used on inhalers report when the inhaler has been used (intentional adherence). We developed a device, INCA^{TM} (12), which assesses inhaler use over time by recording the audio associated with inhaler use. Analysis of the audio data allows inhaler technique errors (which may be considered as un-intentional non-adherence) to be identified. In particular, audio analysis can identify errors such as failing to prime the inhaler, dispersing the medication by exhalation into the inhaler after priming, or failing to generate a sufficient inhalation flow as well as other errors such as dose dumping (13,14). As the acoustic features of inhalation are highly reflective of objectively measured peak inspiratory flow, analysis of the audio recorded to the device can precisely assess medication delivery over time (13,15,16). In addition to providing an assessment of the proficiency of use, analysis of the recorded files provides information on the time of use and the interval between doses (12). Hence, this technology allows the identification and characterisation of an individual's inhaler use and technique over time (both intentional and unintentional non-adherence). To our knowledge no study on inhaler adherence in COPD, assessed by electronic recording devices, has been previously conducted.

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In a landmark study, Vestbo and colleagues found that the least adherent patients in a clinical trial of patients with COPD randomised to receive salmeterol/fluticasone or placebo medication, had higher mortality and hospital readmission rates (17). This association was independent of the study intervention and suggests that poor adherence is associated with critically important but yet unidentified factors other than simply not taking the medication. Hence, it is important to both quantify inhaler adherence and also to understand the determinants of adherence among this population. The objective of this study was to describe the patterns and the determinants of adherence to a commonly used preventer inhaler, salmeterol/fluticasone Diskus ™ inhaler, by patients with COPD.

Some of the results of these studies have been previously reported in the form of an abstract (18).

METHODS

Study design and Setting

This was a prospective observational study of adherence to a regularly prescribed combination long acting beta-agonist/inhaled corticosteroid inhaler by patients with COPD following discharge from hospital. The study was performed in a single centre in the Republic of Ireland and was approved by the Beaumont Hospital Ethical (medical Research) Committee, Dublin, Ireland. The study period was from February 2012 to February 2016. Due to a lack of funding there was a gap in recruitment from June 2012 to January 2014.

Participants

Consecutive patients admitted to hospital for any reason were screened. Eligibility criteria included those who had a known diagnosis of COPD (obstructive spirometry, $FEV_1/FVC<70\%$ or $FEV_1<80\%$), (1) age over 40 years, a smoking history, already prescribed salmeterol/fluticasone Diskus™ inhaler and who had an exacerbation of COPD in the previous year. Eligible patients were approached and those who agreed to participate provided written informed consent.

Variables Collected

At recruitment, data was collected relating to patient age, sex, body mass index (BMI), smoking history, salmeterol/fluticasone dose and reason for admission.

Reason for admission

For this study, reason for admission was divided into two categories 1. Hospital Admission for COPD exacerbation and 2. Hospital Admission not related to COPD, as those admitted due to a COPD exacerbation would likely be considered to have more motivation to use an inhaler on discharge. A COPD exacerbation was defined by a worsening of symptoms (shortness of breath, cough) requiring steroids and antibiotics. Patients categorised as “Hospital Admission not related to COPD” included

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those with a previous diagnosis of COPD who were admitted to hospital for an unrelated cause (i.e. surgical admission).

Disease Severity

To evaluate COPD severity, data on the number of COPD admissions in the previous year and pulmonary function (FEV_1 (L) and % predicted) was collected and Cough Peak Expiratory Flow (cough PEF L/min, Mini-Wright Clement Clarke International LTD) was measured. Patients were asked to complete the COPD Assessment Test (CAT) and to score their dyspnoea on the Medical Research Council (MRC) Dyspnoea Scale (1 to 5, 1 not limited and 5 unable to leave the home due to breathlessness). With this information patients were classified into GOLD defined grades. (1).

Personal Factors

Co-morbid medical history (using the Charlson Co-Morbidity Score (19)) and the number of regular medications currently prescribed were recorded. Information on cognitive function (Montreal Cognitive Assessment, MoCA (20)) and psychological status (Hospital Anxiety Depression, HAD Score (21)) was recorded. Health literacy was assessed using the European Health Literacy Survey (EHLS) (22) and patient's beliefs in medicine were assessed by the Beliefs in Medication Questionnaire (BMQ, with a score >50 indicating negative beliefs in medicine (23)).

In addition, data on the patient's level of social support were collected. This included data pertaining to levels of governmental support for healthcare cost, social isolation (i.e. who lives at home alone, does the patient have a carer) and frailty (i.e. does the patient have a chairlift, a bedroom downstairs, meals delivered or need a carer). A categorical variable, "isolation", was created as follows: 1 = Not Alone + Carer, 2 = Not Alone + No Carer, 3 = Alone + Carer, 4= Alone + No Carer; A categorical variable, "frailty" was created as follows: 1= Need a Chair lift, 2 = Bedroom Downstairs, 3 = Bedroom Downstairs/Need a Chair Lift + Meals delivered to the Home, and 4 = Bedroom Downstairs/Need a Chair Lift + Need of a Carer +/- Meals delivered home.

Objective measurement of inhaler adherence and technique using the INCA™ device

An INCA™ audio recording device was attached to a salmeterol/fluticasone Diskus™ inhaler to objectively assess both time of use and technique of inhaler use. Each time a patient opened their inhaler, a digital audio recording was made. These recordings were used to calculate the time of use, the interval between doses and the proficiency of inhaler use. Further details of the design and validation of the INCA™ device have been previously reported (12,24).

In hospital, patients were repeatedly shown how to use the inhaler by the ward staff each time the medication was dispensed, as per written Hospital Policy. Inhaler proficiency was also assessed using a checklist on inhaler use, the Inhaler Proficiency Score (25,25,26).

At recruitment, patients were given a new 60-dose salmeterol/fluticasone Diskus™ inhaler with an attached INCA™ device, for one month of use. On discharge, they were asked to continue using their inhaler as they had been shown, twice per day, and were told that between 26 and 30 days later they would be contacted and a courier would collect their inhaler.

Calculation of adherence

Two independent raters assessed the acoustic recordings for evidence of critical errors, as previously described (12-14). The inter-rater agreement was 88.4%. The raters did not have any involvement in any data analysis beyond rating the audio files. Information on the time, interval between doses and technique of inhaler use were combined to calculate an area under the curve (AUC) metric, using a trapezoidal function. This method of calculating adherence has previously been described (24). Initially, the AUC is calculated for the expected doses. Following this, the AUC is calculated for the participant's Attempted Adherence (audio files where there was evidence of drug priming), where non-attempted adherence demonstrate intentional non-adherence. Removing doses where a critical technique error (i.e. failing to prime the inhaler, exhalation into the inhaler after priming and before

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inhalation, or generating a low inspiratory flow) allows for calculation of the Actual Adherence, a combination of intentional and un-intentional non-adherence.

Statistical Analysis

All categorical variables were summarized using the number of observations, and percentage of patients. Continuous variables were summarised using mean (SD) and ordinal data with median (IQR). In cases where data were not normally distributed a log transformation was performed to achieve normality. These data were analysed on a log scale and all results were back transformed. Between-group comparisons (e.g. reason for admission) were made with an unpaired t-test, ANOVA, Chi-squared test and Mann-Whitney test where appropriate. Clustering was performed using an agglomerative hierarchical method, employing the wards-linkage function with squared Euclidian distance (27). This method was chosen over single-linkage clustering as it is more robust to noise in the data. Qualitatively similar results were also obtained using average-linkage clustering. The number of clusters was chosen from inspection of the cluster dendrogram. Before clustering, variables were rescaled to have equal variance. This is required for algorithms employing a distance-based metric. A multinomial logistic regression was used to compare the different cluster groups in an attempt to predict cluster membership.

RESULTS

Participants

Over the study period, 265 patients consented to participate. Complete data on both baseline variables and electronically recorded adherence were available for 204 patients, see flow diagram, Figure 1.

The characteristics of the patients are shown in Table 1. The participants were elderly, mean age 71 (SD=9.8) years with a mean FEV_1 of 1.3L, 52% predicted. In addition to COPD, they had a significant burden of other medical diseases with a mean Charlson co-morbidity score of 6 and further, were prescribed a median of 12 medications. One fourth were socially isolated (Isolation score> 2) and over a third had indices of frailty (Frailty score >2). Forty seven percent of the patients had evidence of mild cognitive impairment, MoCA score (19-24) and a further 33% had moderate cognitive impairment, with a MoCA score less than 19. Other than features regarding the severity of COPD and indices of isolation/frailty, there were no significant differences in the characteristics of the patients admitted with an exacerbation of COPD and those admitted with another cause, see Table 1.

Adherence to a twice-daily preventer inhaler

Using the AUC method (mentioned in the methods section) to calculate adherence the median (IQR) and mean (SD) Actual Adherence over the study period was 6% (42.0) and 22.9% (29.1) of what would be expected if all the doses had been taken correctly and on time. Only 7% of the study population had an Actual Adherence over 80%. There was no difference in the Actual Adherence between those who were discharged following an exacerbation of COPD, median (IQR) 6% (47%), mean (SD) 23.6% (29.4) and those COPD patients who had another reason for admission, median (IQR) 6% (32%) and mean (SD) 22.2% (29.2), p=0.74.

Analysis of the digital audio data indicated that most patients intermittently or frequently made errors in inhaler handling in the month after hospital discharge, despite reasonably good inhaler technique on discharge with a mean inhaler checklist (IPS) score of 8 out of a possible 10. The most common error

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made was low inhalation flow, (Peak Inspiratory Flow <35L/min); see Figure 2(d) and (e). Of the total 8133 audio files recorded to the INCA^{TM} device, this error occurred in 1941 (24%) inhalations. A further 984 (12%) made repeated short inhalations, termed multiple breaths. Exhalation into the inhaler after priming the dose and before inhalation occurred in 277 events (3.4%), see Figure 2(a) and (c). There were 30 audio files (0.03%) with evidence of more than 1 drug blister suggestive of dose wasting. See Figure 3 for a distribution of inhaler technique errors.

Analysis of the time of inhaler use indicated that, in contrast to the instruction that the inhaler was to be used twice per day twelve hours apart, most patients used the inhaler irregularly during the month following discharge. There were both periods of excessive dosing (≥3 doses in 24 hours) and periods of missed doses (<2 doses in 24 hours), see Table 2 and Figure 2 (b), (d), (f) and (g). Only 10 patients (5%) never attempted to use their inhaler and 29 patients (14%) used their inhaler less than 20% of the time (i.e. 2 to 3 times a week). See Figure 4 for a summary of all adherence measures calculated.

Patterns of inhaler use

There was wide variability in inhaler use by the participants, as we have seen in other populations (12,24,28), therefore, we sought to characterise inhaler adherence by patterns. Adherence patterns were characterised using clustering of the Attempted Adherence AUC and the technique error rate. Hierarchical clustering found three well-separated clusters of approximately equal size corresponding to distinct patterns of behaviour. The characteristics of the three groups are shown in the online supplement, eTable 1. Cluster 1, n=70 (34%), was characterised by low Attempted Adherence (mean=18%), intentional adherence, and high error rate (88%), un-intentional non-adherence. Cluster 2, n=63 (31%), showed high Attempted Adherence (76%), intentional adherence, coupled with high error rate (73%), un-intentional non-adherence, leading to poor Actual Adherence (20%). While Cluster 3, n=61 (30%), contained patients with better overall adherence, characterised by high Attempted Adherence (58%), intentional adherence and low error rate (8%), un-intentional non-adherence. Ten patients with zero Attempted Adherence were excluded from the cluster analysis; see Table 3 and Figure 5.

Determinants of adherence

Demographic and clinical measures predictive of cluster membership were investigated using a multinomial logistic regression, with good adherence (membership of Cluster 3) taken as the base outcome. Co-morbidity was strongly predictive of membership of both Clusters 1 and 2, suggesting a contribution to poor technique, while cough PEF, age and MoCA were predictive of membership of Cluster 1, corresponding to poor Attempted Adherence and high technique error rate. FEV_1 was predictive of membership of cluster 2 (good Attempted Adherence, poor technique), but not cluster 1, suggesting lung function makes a contribution to technique errors in those with good Attempted Adherence. See Table 4 for a summary of these results.

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DISCUSSION

In the month following discharge from hospital only 7% of patients with severe COPD used their preventer inhaler therapy regularly and with correct technique more than 80% of the time. By contrast, 31% used the inhaler regularly but made consistent errors, despite repeated instruction in hospital over 30% rarely used the inhaler and when they did so, they often used it incorrectly. The major factors determining adherence were the presence of severely impaired lung function, which affected the inhalation flow, and the patient's cognitive status which may have affected the patient's ability to remember both when and how to use the inhaler.

Re-admission following an exacerbation of COPD has become a measure of quality of care (29,30). Vestbo et al. found that hospital readmission with a COPD exacerbation was lower amongst those patients with better adherence (17). It is essential, therefore, that strategies to reduce re-admission include emphasis on good adherence to maintenance inhaled medications and correct inhaler use. Currently, there is little information on the factors that influence adherence among COPD patients in this setting (following a hospital admission). The design of successful adherence interventions requires a detailed understanding of the determinants of adherence in the population being targeted. Hence, we chose to study adherence in COPD patients being discharged from hospital.

The determinants studied were based on the information in the published literature (17,31-36). One model, the COM B framework of adherence, groups adherence determinants under the themes of comprehension, opportunities and motivation (37). Hence, for COPD patients, their comprehension and capacity to remember and follow instructions, their motivation (which can be affected by the patient's beliefs about medicine and illness), depression, social isolation, frailty and health status may impact on adherence (32,38-40). Lost opportunities for patient learning may also arise either because of poor healthcare professional communication, poor knowledge of inhaler handling leading to poor instruction, or a patient's poor comprehension as a result of lower health literacy (41). We used a variety of validated instruments to evaluate each of these themes and we included information on

measures of lung function, as we have previously shown that low inhalation flow is a common error in inhaler handling (12,24,28).

Analysis of the information recorded to the INCA™ device identified that most patients made errors in both inhaler use and technique. We used cluster analysis to categorise the patients into groups based on regularity and proficiency of use. Knowledge of these patterns of inhaler use could be used to develop personalised interventions to promote adherence. For example, those who use their inhaler well and on time need encouragement, while those who use the inhaler regularly but with incorrect technique would benefit from an intervention addressing this issue. Patients who are largely forgetful may benefit from a reminder based system (9) or an intervention such as motivational interviewing (42).

The results of this study show that poor cognitive function is an important determinant of adherence. Cognitive impairment is increasingly being recognised in patients with COPD. For example, brain imaging studies have shown significant white matter pathology in the fronto-striatal regions, areas which impact on planning, problem solving, and prospective memory capacity (43,44). Patients with poor executive functioning often display a "knowing-doing discrepancy". While they can report specific instructions they cannot translate these into specific behavioural and motor plans and activity. Hence, abnormalities in the executive and memory domain may influence adherence through poor recall of inhaler technique and not remembering to use their inhaler.

The most common technique error identified in this study was low peak inspiratory flow, which occurred in 24% of all inhalations. For dry powder inhalers, the user is required to generate a sufficient inspiratory flow to de-agglomerate the particles for the inhaler to be effective. For many patients, particularly those experiencing increased hyperinflation during and after an exacerbation of COPD, it may not be possible to generate sufficient airflow for effective inhalation, leading to ineffective drug delivery. In our study, we found FEV1 and cough PEF to be predictive of a high technique error rate and thus poor overall adherence. Low cough PEF could be the result of a number of aspects of severe COPD such as muscle weakness, airflow limitation and/or the effect of air

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trapping (45,46) Regardless of the exact mechanism, the low cough PEF seen in this cohort indicates the severity of the underlying lung condition and the ability of the patient to inhale with sufficient pressure to overcome the internal resistance of the dry powder inhaler.

There are several limitations to this study. This was a single centre study observational study with no control arm and the findings of the study should be interpreted with this in mind. Additionally, the majority (98%) of patients enrolled in this study held government sponsored health insurance, which is reflective of our cohort's age group. Whilst some patient characteristics of this cohort are quite different to those studied in randomised control trials of stable outpatient COPD (47), they are similar to those in recent observational cohort studies of hospital recruited COPD patients in the UK and USA(2,4,5,48,49). Therefore, it is likely that our results are representative of similar patients in other health systems. In addition, with regard to poor inspiratory flow, we are unable to say if this was due to impaired lung function or poor effort. However, this was not the aim of this study and future qualitative studies looking at factors related to adherence and interventional studies will address this issue.

As this study only analysed adherence over a one-month period, we do not know if adherence influences re-admission or if adherence patterns change over time. To address this we are performing a 3-month extension of this study to assess the relationship of adherence to future healthcare use. A further limitation of this study was that only one pharmacological medication delivered by one device was studied, namely the salmeterol-fluticasone Diskus™ inhaler. When we first developed the INCA™ device we used it with the Diskus™ device as, at the time, this was the most commonly used treatment for patients with COPD. However, given that we were studying a behaviour that would likely be repeated by this patient group with other inhalers, we believe that the results can be generalised, although further study is warranted to investigate this. We provided the adapted inhaler with the INCA™ device attached and hence, deliberately concentrated on the implementation phase of adherence (50) In doing so, we may have not identified other determinants of adherence affecting the initiation or persistence phases of adherence, such as cost and access to pharmacy service to obtain medications(2). The technology is also limited by the fact that the patient has to return the inhaler and

device and the audio files have to be manually reviewed for the adherence to be calculated. However, an automated algorithm that can analyse these audio files has been validated in a cohort of asthma patients and will be validated in a COPD cohort (14,51,52) Additionally, patients were aware that their adherence was being monitored for the month of the study which may lead to increased adherence. However, adherence remained poor and suggests that adherence in a real world population may even be worse.

There are several novel aspects to this study, including the measurement of adherence immediately following discharge from hospital, the description of novel patterns of adherence using analysis of data collected to a system that evaluated all aspects of inhaler use and the identification of novel determinants of adherence in this patient cohort. Additionally, this study was performed in a 'real world' population. However, this technology and methodology can also be utilised in a clinical trial setting and has potential use as an education tool to improve inhaler use and technique in clinical practice for patients and clinicians.

There has been a proliferation of devices delivering inhaled medications in the last few years, which has challenged clinicians to train patients how to use theses devices correctly. Pharmaceutical companies developing these devices should be mindful of creating easy to use fail-proof devices so as not to overburden patients and clinicians with the responsibility of learning the nuances of correct inhaler technique.

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Conclusion

The results of this study suggest that only 7% of patients with severe COPD had an adherence rate >80% following discharge from hospital. The major determinants of poor adherence were the presence of cognitive impairment, which affected the patient's ability to remember to take the medication and severe hyperinflation, which affected the ability of the individual to generate sufficient inhalation flow and as a consequence resulted in impaired drug delivery.

TABLE 1: The clinical features of the cohort including the demographics, COPD features, personal and socio-economic factors. Data for all patients in the cohort, as well as patients who were admitted to hospital with an exacerbation of COPD and those who had COPD but were admitted for other reasons are shown. All values are presented as mean (SD) except where indicated. BMI, body mass index; FEV_1, forced expiratory volume; Cough PEF, cough peak expiratory flow; CAT score, COPD assessment test ; MoCA, Montréal cognitive assessment; *Isolation Score and ^frailty scores were calculated as described in the methods section.

	All Patients	COPD Exacerbation	Not COPD Exacerbation	p value
DEMOGRAPHICS	(n=265)	(n=168)	(n=97)	
Mean Age	70.6 (9.8)	70.2 (10.1)	71.2(9.2)	0.41
Sex (% Female)	53%	57%	47%	0.15
BMI	27.5 (6.6)	26.7 (6.5)	29.0 (6.6)	0.05
Median Pack Years smoked (IQR)	47.0 (47.1)	47.0 (43.5)	47.0 (50.0)	0.99
Currently smoking (%)	22%	25%	18%	0.22
Salmeterol/fluticasone Dose (% 500mcg)	75%	77%	71%	0.28
Inhaler Proficiency Score (range 0-10)	7.6 (1.6)	7.5 (1.5)	7.6 (1.7)	0.69
DISEASE SEVERITY				
FEV_1 (L)	1.3 (0.6)	1.2 (0.6)	1.5 (0.6)	<0.01
FEV_1 (%)	51.7 (21.3)	49.0 (20.3)	57.7 (22.3)	<0.01
Cough PEF	159.6 (99.2)	150.60 (87.7)	173.1 (112.3)	0.09
CAT score	20.5 (7.9)	21.2 (7.7)	19.3 (8.1)	0.06
Number of COPD admissions in previous year	1.3 (1.7)	1.8 (1.8)	0.7 (1.2)	<0.01
Median MRC dyspnoea score (IQR)	3.6 (1.1)	3.6 (1.1)	3.5 (1.1)	0.27
Number in GOLD Grade (%)				
A	3 (1)	0 (0)	3 (3)	0.02
B	56 (21)	0 (0)	56 (58)	<0.01
C	5 (2)	4 (2)	1 (1)	0.47

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D	201 (76)	164 (98)	37 (38)	<0.01
PERSONAL FACTORS				
Charlson Co-Morbidity	5.9 (1.8)	5.7 (1.7)	6.2 (2.0)	0.06
Median No. of Regular Medications (IQR)	12 (7)	11 (8)	12 (7)	0.11
Median No. of Nebulised Treatment (IQR)	1 (1.5)	1 (1)	1 (1)	<0.01
MoCA score (range 0-30)	20.2 (6.2)	19.9 (6.2)	20.7 (6.2)	0.36
HADS Total score (range 0-14)	12.9 (7.5)	12.8 (7.5)	13.0 (7.5)	0.81
Anxiety component of HADS (range 0-7)	6.9 (4.6)	6.7 (4.4)	7.2 (4.9)	0.44
Depression component of HADS (range 0-7)	5.6 (4.1)	5.5 (4.2)	5.8 (3.9)	0.51
European Health Literacy Score (range 16- 80)	33.7 (10.7)	33.7 (10.1)	33.8 (11.6)	0.94
Beliefs in Medicine Questionnaire (range 18-90)	52.0 (10.7)	52.2 (11.3)	51.9 (10.2)	0.89
Median Isolation Score (IQR)*	2 (1)	2 (0)	2 (2)	<0.01
Patients with Government Sponsored Health Insurance (%)	98%	98%	99%	0.56
Median Frailty Score (IQR)^	2 (2)	2 (2)	2 (2.5)	0.47

TABLE 2: Frequency of different types of errors based on analysis of the recordings made to the INCA™ device over one month of use. The data shown reflects the various ways that patients may misuse an inhaler. Specifically, attempted doses represents audio files where the patient attempted to take their medication (i.e. evidence of drug priming). Technique errors included the following critical errors in inhaler handling: blistering but no inhalation, inhalation flow less than 35L/sec, multiple short inhalations and exhalation into the inhaler after priming. Extra dosing, is defined as 3 or more doses in a 24 hour period, missed doses as <2 doses in a 24 hour period. The total number of errors and the median and mean rates are shown below.

	Attempted Doses	Technique Errors	Extra Doses	Missed Doses
Total Number	8133	4103	778	4568
Median per person (IQR)	46 (32)	15 (27)	3 (4)	17 (27)
Median Rate (IQR)	62.5 (49.5)	12 (34)	6.7 (13.3)	33.1 (40.7)
Mean Rate% (SD)	59.4 (30)	24.3 (27.5)	10.7 (12.4)	38.6 (26.7)
Number of people (%) with >20% & <50% Mean Rate	69 (34)	50 (24)	30 (15)	68 (33)

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TABLE 3: Mean (SD) of different adherence measures calculated from the INCA™ device for the three clusters was calculated. p values are obtained from one-way ANOVA of each variable across the three groups. Cluster 1 were patients with poor Attempted Adherence and poor inhaler technique. Cluster 2 were patients with good Attempted Adherence and poor inhaler technique. Cluster 3 were patients with good Attempted Adherence and good inhaler technique.

	CLUSTER 1 *Poor Attempted Poor Technique* n=70	**CLUSTER 2** *Good Attempted Poor Technique* n=63	**CLUSTER 3** *Good Attempted Good Technique* n=61	P value
ADHERENCE				
Actual Adherence (%)	1.73 (2.77)	19.5(19.6)	54.6 (28.5)	<0.01
Attempted Adherence (%)	18.1 (13.5)	76.1 (16.7)	58.5 (29.2)	<0.01
Technique Error Rate (%)	88.1 (17.2)	73.2 (24.8)	7.72 (8.63)	<0.01

TABLE 4: Multinomial logistic regression of adherence cluster membership against demographic and clinical factors. The reference category is good adherence (cluster 3). All variables have been standardised to unit variance to enable comparison of effect sizes. The coefficients represent the change in log-odds of cluster membership per unit increase in the associated variable. Overall the model fit was highly significant (Likelihood-Ratio Chi-square test, $p < 0.00005$, pseudo-R^2=0.204).

Adherence Cluster Group	Variable	Relative Risk Ratio	Std. Err.	p value
Cluster 1				
Poor Attempted	MoCA	0.508	0.175	0.049
Poor Technique	Cough PEF	0.21	0.089	<0.001
	FEV_1	1.263	0.408	0.47
	Co-Morbidity	4.279	2.026	0.002
	Age	0.352	0.155	0.018
	Constant	1.598	0.552	0.174
Cluster 2				
Good Attempted	MoCA	0.786	0.274	0.489
Poor Technique	Cough PEF	0.728	0.234	0.322
	FEV_1	0.536	0.166	0.045
	Co-Morbidity	3.458	1.609	0.008
	Age	0.604	0.263	0.246
	Constant	1.509	0.51	0.224

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FIGURE LEGENDS

FIGURE 1: Study Flow: During the study period, 265 patients with COPD were recruited. Due to lost devices, device failures and patients passing away, there was adherence data on 204 patients.

FIGURE 2: Examples of Different Inhaler use Figure (a) is an example of an inhaler returned from a patient who persistently exhaled into the device before inhaling, introducing moisture into the mouthpiece. The image clearly shows clumped drug deposition in the mouth piece, i.e. wasted medication. Figures (b) to (g) are graphical representations of adherence data collected from the INCA^{TM} device over time (hours of the day on the y-axis and date on the x-axis). Each mark on the graph indicates a dose taken; a green dot indicates good technique while an orange diamond indicates poor inhaler technique. Figure (b) is a patient who was given the adapted inhaler for the day before discharge. Following their discharge home this patient, for the most part, only took their medication once daily. Figure (c) is the adherence data for the patient who made the persistent error of exhaling into the inhaler after drug priming and before inhalation leading to drug clumping (a). Figure (d) is an example of a patient who was overusing their inhaler, although with poor technique (low inspiratory flow) and then subsequently stopped using their inhaler for several weeks. Figure (e) is a patient who took their inhaler every day with good interval between doses but with a persistent technique error, low peak inspiratory flow. Figure (f) is an example of a patient who rarely took their medication, and when they did it was with poor inspiratory flow. Figure (g) is an example of a patient who took their inhaler regularly and correctly for several days and then just stopped taking their medication for 2 weeks.

FIGURE 3: Inhaler Technique Errors. The most common technique error in this cohort of COPD patients was low peak inspiratory flow (PIF) followed by multiple inhalations (i.e. poor breath hold) and multiple errors (i.e. more than one error in an audio file).

FIGURE 4: Different Adherence Measures Calculated. Figure (a) displays the difference in adherence calculated from the dose counter (Average Adherence) and the measures from the INCA™ device, the Attempted Adherence (how frequently the patient tried to take their inhaler) and the Actual Adherence (accounting for time of use, interval between doses and technique of use). There was a significant difference between the Average Adherence and the Actual Adherence, $p<0.01$. There was a significant difference between the Average Adherence and the Attempted Adherence, $p<0.01$, due to patients performing multiple blisters in one dose and dose dumping. Figure (b) displays the high levels of missed doses, over dose and technique errors in this cohort of COPD patients. (*$p<0.01$)

FIGURE 5: Different Inhaler Use Patterns. Figure (a) is a dendrogram resulting from the cluster analysis using Ward's method in 204 patients with COPD leading to 3 major clusters. Figure (b) is a distribution of the three clusters based on Attempted Adherence and technique error rate. Cluster 1 represents patients with poor Attempted Adherence and high technique error rate, leading to a low Actual Adherence. Cluster 2 represents patients with good Attempted Adherence and high technique error rate (i.e. Figure 2(e)). Cluster 3 represents patients with good Attempted Adherence and low technique error rate leading to a high Actual Adherence.

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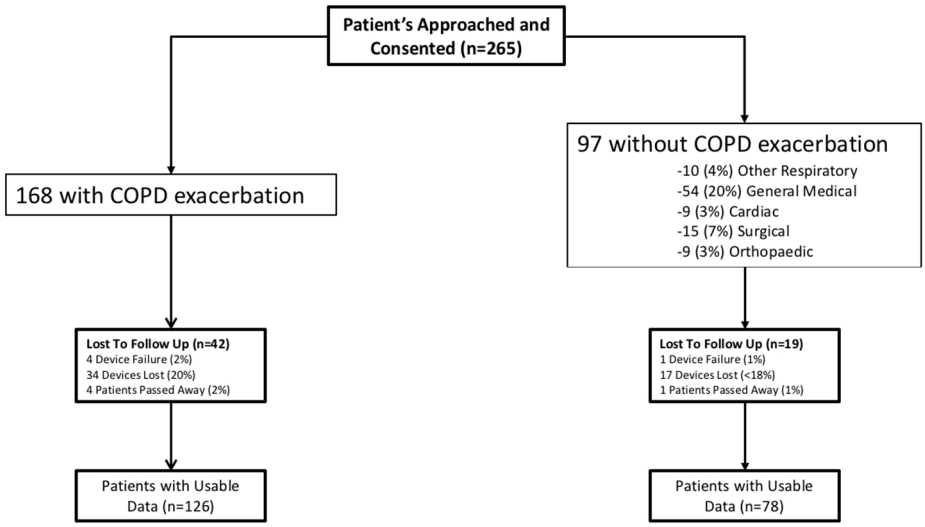

FIGURE 1: Study Flow: During the study period, 265 patients with COPD were recruited. Due to lost devices, device failures and patients passing away, there was adherence data on 204 patients.
Figure 1
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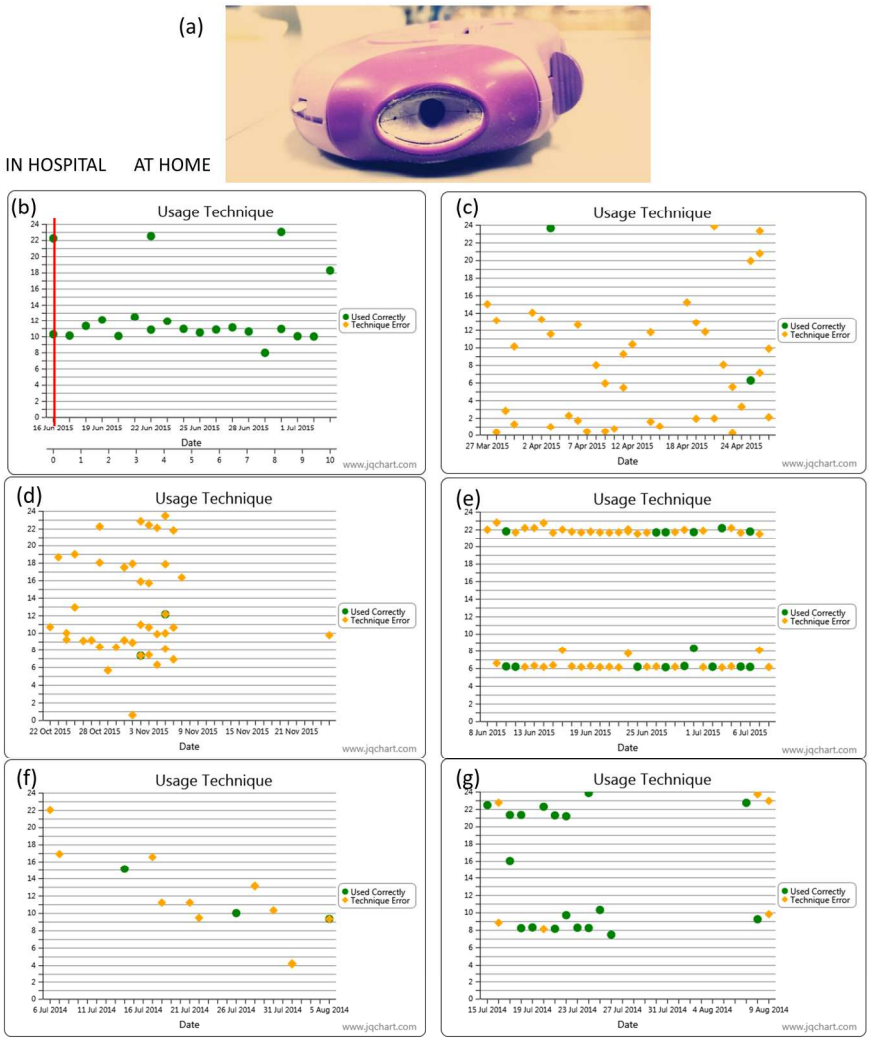

FIGURE 2: Examples of Different Inhaler use Figure (a) is an example of an inhaler returned from a patient who persistently exhaled into the device before inhaling, introducing moisture into the mouthpiece. The image clearly shows clumped drug deposition in the mouth piece, i.e. wasted medication. Figures (b) to (g) are graphical representations of adherence data collected from the INCATM device over time (hours of the day on the y-axis and date on the x-axis). Each mark on the graph indicates a dose taken; a green dot indicates good technique while an orange diamond indicates poor inhaler technique. Figure (b) is a patient who was given the adapted inhaler for the day before discharge. Following their discharge home this patient, for the most part, only took their medication once daily. Figure (c) is the adherence data for the patient who made the persistent error of exhaling into the inhaler after drug priming and before inhalation leading to drug clumping (a). Figure (d) is an example of a patient who was overusing their inhaler, although with poor technique (low inspiratory flow) and then subsequently stopped using their inhaler for several weeks. Figure (e) is a patient who took their inhaler every day with good interval between doses but with a persistent technique error, low peak inspiratory flow. Figure (f) is an example of a patient who

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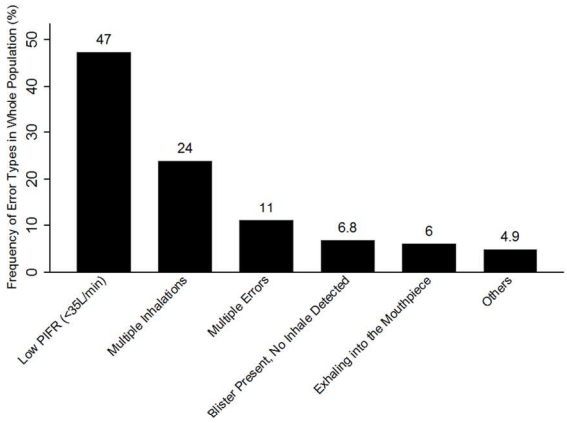
Figure 2

254x338mm (300 x 300 DPI)



Error Type	Number	Mean per patient (SD)	Range
Low PIFR <35L/min	1941	9.6 (14)	0-60
Multiple Inhalations	984	4.5(11)	0-58
Multiple Errors	454	2.2 (7)	0-56
Blister Present, No Inhale Detected	279	1.4 (5)	0-47
Exhaling into the mouthpiece	246	1.2 (3.5)	0-34
Others	199	1.0 (2.9)	0-28
TOTAL ERRORS	**4103**	**20.2 (18)**	**0-60**

FIGURE 3: Inhaler Technique Errors. The most common technique error in this cohort of COPD patients was low peak inspiratory flow (PIF) followed by multiple inhalations (i.e. poor breath hold) and multiple errors (i.e. more than one error in an audio file).
Figure 3
158x99mm (300 x 300 DPI)

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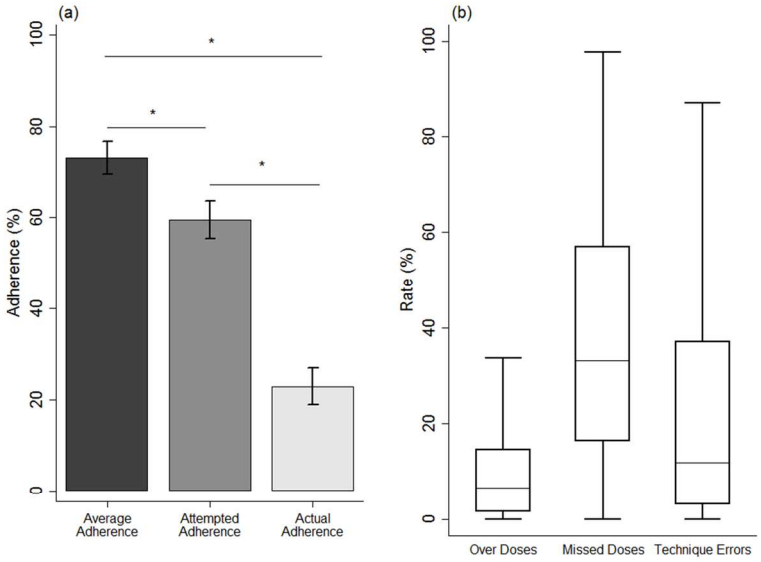

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158x99mm (300 x 300 DPI)

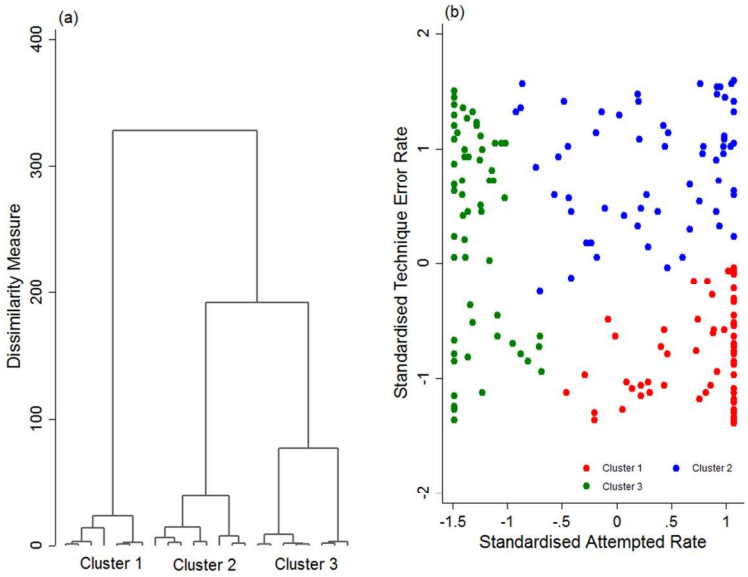

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Figure 5
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ONLINE SUPPLIMENTARY MATERIAL 1

eTABLE 1: The clinical features of the three clusters including the demographics, COPD features, personal and socio-economic factors. All values are presented as mean (SD) except where indicated. BMI, body mass index; FEV_1, forced expiratory volume; Cough PEFR, cough peak expiratory flow rate; CAT score, COPD assessment test ; MoCA, Montréal cognitive assessment; *Isolation Score and ^frailty scores were calculated as described in the methods section.

	CLUSTER 1 *Poor Attempted Poor Technique*	**CLUSTER 2** *Good Attempted Poor Technique*	**CLUSTER 3** *Good Attempted Good Technique*	p value
DEMOGRAPHICS	(n=70)	(n=63)	(n=61)	
Mean Age	71.4 (9.3)	69.2 (8.9)	67.6 (9.8)	0.49
Sex (% Female)	61%	43%	51%	0.10
BMI	27.0 (7.0)	27.6 (7.2)	28.1 (5.4)	0.05
Pack Years smoked	53.9 (43.5)	64.8 (50.5)	50.7 (30.4)	0.75
Currently smoking (%)	29%	23%	15%	0.19
Salmeterol/fluticasone Dose (% 500mcg)	67%	78%	82%	0.14
Inhaler Proficiency Score (range 0-10)	7.2 (1.7)	7.6 (1.7)	8.0 (1.4)	0.20
DISEASE SEVERITY				
FEV_1 (L)	1.3 (0.6)	1.2 (0.7)	1.4 (0.7)	0.35
FEV_1 (%)	54.7 (22.4)	48.3 (20.4)	55.1 (23.6)	0.63
Cough PEFR	121.6 (81.0)	184.8 (111.3)	199.8 (108.8)	<0.01
CAT score	20.6 (8.1)	18.9 (7.0)	22.4 (7.6)	0.56
Number of COPD admissions in previous year	1.6 (1.7)	1.2 (1.8)	1.3 (1.5)	0.09
Median MRC dyspnoea score (IQR)	3 (1)	4 (1)	4 (1)	0.25
Number in GOLD Grade (%)				
A	0 (0)	1 (2)	0 (0)	0.33
B	14 (20)	10 (15)	12 (20)	0.76

C	1 (2)	1 (2)	0 (0)	0.60
D	55 (78)	51 (81)	49 (80)	0.93
PERSONAL FACTORS				
Charlson Co-Morbidity	6.2 (2.1)	5.9 (1.3)	5.4 (1.8)	0.05
Median No. of Regular Medications (IQR)	12 (6)	12 (7)	11 (9)	0.96
Median No. of Nebulisers used (IQR)	1 (1)	1 (0.5)	1 (1)	0.36
MoCA score (range 0-30)	18.1 (7.0)	22.1 (4.6)	23.1 (4.7)	<0.01
HADS Total score (range 0-14)	13.0 (7.3)	10.9 (6.1)	13.5 (7.6)	0.69
Anxiety component of HADS (range 0-7)	7.0 (4.5)	6.4 (4.3)	7.0 (4.4)	0.69
Depression component of HADS (range 0-7)	5.9 (4.4)	4.6 (2.9)	5.8 (4.1)	0.92
European Health Literacy Score (range 16- 80)	36.8 (11.3)	31.6 (8.0)	32.8 (10.5)	0.61
Beliefs in Medicine Questionnaire (range 18-90)	49.9 (10.3)	53.9 (9.8)	50.5 (11.8)	0.66
SOCIO-ECONOMIC DETAILS				
Patients Living Alone (%)	26%	26%	19%	0.63
Patients with a Carer (%)	16%	20%	18%	0.80
Number of Floors in Home	1.8 (0.5)	1.9 (0.4)	1.8 (0.5)	0.41
Patients with a Stair Lift (%)	20%	24%	14%	0.55
Patients with Downstairs Bathroom (%)	29%	24%	27%	0.77
Patients with Downstairs Bedroom (%)	52%	41%	47%	0.80
Patients who get Meals Delivered (%)	3%	4%	4%	0.99
Median Isolation Score (IQR)*	2 (1)	2 (1)	2 (0)	<0.01
Patients Isolation Score* >2 (%)	26%	27%	19%	0.59
Patients with Government Sponsored Health Insurance (%)	100%	100%	95%	0.86
Median Frailty Score (IQR)^	2 (1)	2 (3)	2 (2)	0.31
Patients Frailty Score >2 (%)	14%	35%	42%	0.13